

**Bohn, Brent**

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**From:** Cowden, John  
**Sent:** Tuesday, June 17, 2014 4:12 PM  
**To:** Powers, Christina  
**Cc:** Lee, Janice; Sams, Reeder; Jones, Ryan  
**Subject:** FW: Updated As lit search flow diagram (with Jan-Mar 2014 lit search update)  
**Attachments:** Arsenic\_Lit\_Diagram\_6-12-2014.pptx

Hey Christy,

Happy Tuesday (again)! I heard you might be looking for a lit flow diagram.... ☺

Have a great evening!

John

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**From:** Burch, Dave [mailto:dave.burch@icfi.com]  
**Sent:** Thursday, June 12, 2014 4:01 PM  
**To:** Cowden, John; Lee, Janice; Sams, Reeder  
**Cc:** Turley, Audrey  
**Subject:** Updated As lit search flow diagram (with Jan-Mar 2014 lit search update)

John,

Attached is a revised version of the literature search flow diagram for arsenic, now updated to show the disposition of the additional references retrieved via the lit search update for January-March 2014. Please use this version in any updated documents describing the methods and results of the systematic literature review supporting the arsenic assessment.

Give me a call if you have any questions.

Thanks,  
Dave

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## APPENDIX

THE FOLLOWING TABLES SHOW THE RESULTS OF THE ANALYSES OF THE

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**From:** Cowden, John  
**Sent:** Tuesday, June 17, 2014 11:25 AM  
**To:** Powers, Christina; Korrane, Ellen; Lee, Janice; Rooney, Andrew (NIH/NIEHS) [E]; Thomas, David; Sams, Reeder; Jones, Ryan; Luben, Tom  
**Subject:** Revised slides for the arsenic bimonthly meeting  
**Attachments:** IRIS June Bimonthly Public Meeting\_arsenic - draft - 06.17.14.pptx

Hi Christina, Ellen, Janice, Andy, Dave, Reeder, Ryan, and Tom,

Happy Tuesday! I hope that things are going well for you today.

We got some feedback yesterday on our slides. Basically, they wanted all of the discussion points/NRC recommendations related to a science issue on a single slide. And bigger font. MUCH bigger font. To accommodate these suggestions, the text had to be abbreviated to fit. So, the text is BIGGER and SHORTER at the same time! ☺

I am still hoping to frame the discussions around NRC recommendations. The NRC recommendations are now table headings (in blue/white) and relevant discussion points are underneath them. Take a look at the slides and see if the revisions make sense (Christy, I tried to capture your MOA revisions from this morning, let me know how I did).

Let me know if you have any questions. And thanks for all of you help pulling these materials together.

Have a great afternoon!

John

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**From:** Cowden, John  
**Sent:** Friday, June 13, 2014 5:26 PM  
**To:** Sams, Reeder; Lee, Janice; Powers, Christina; Luben, Tom; Korrane, Ellen; Thomas, David; Jones, Ryan; Rooney, Andrew (NIH/NIEHS) [E]  
**Subject:** Draft iAs presentation for IRIS bimonthly meeting  
**Attachments:** IRIS June Bimonthly Public Meeting\_arsenic - draft - 06.13.14.pptx

Hi Christina, Ellen, Janice, Andy, Dave, Reeder, Ryan, and Tom,

Happy Friday! I hope that things are going well for you today.

Based upon our conversations, I made some revisions to the presentation. You'll see that the presentation is now 21 slides. Don't freak out - it's just an artifact of the presentation strategy. Using multiple slides for the questions will allow for much easier reviewin/editing as well.

I tried to organize the questions around NRC recommendations, with discussion points stemming from each recommendation. Feel free to make revisions to the discussion points or add ones you'd like to see. The slides could probably use a thorough Rooney Review too! ☺

Thanks for all of you help pulling these materials together. We're excited to share our work with the public!

Have a great weekend!

John

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**From:** Sams, Reeder  
**Sent:** Thursday, June 12, 2014 10:59 AM  
**To:** Thomas, David; Andrew Rooney; Luben, Tom; Kirrane, Ellen; Powers, Christina  
**Subject:** FW: Arsenic comment from the docket  
**Attachments:** EPRI 6-11-14 comment Arsenic.pdf

FYI- there will likely be more comments in the next day or so

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**From:** Samuels, Crystal  
**Sent:** Thursday, June 12, 2014 10:37 AM  
**To:** Sams, Reeder; Burgoon, Lyle; Chiu, Weihsueh; Lee, Janice; Cowden, John  
**Cc:** DeSantis, Joe  
**Subject:** Arsenic comment from the docket

Good morning,

Attached is a comment on the FDMS side of the docket that is pending post for Arsenic. It will become visible in regulation.gov, but you might want to see now. Please let me know if you have any questions.

**COMMENTS ON DRAFT DEVELOPMENT MATERIALS FOR THE  
INTEGRATED RISK INFORMATION SYSTEM (IRIS) TOXICOLOGICAL  
REVIEW OF INORGANIC ARSENIC**

**Docket ID: EPA-HQ-ORD-2012-0830**

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June 11, 2014

The Electric Power Research Institute (EPRI) is pleased to provide the following comments on the Draft Development Materials for the IRIS Toxicological Review of Inorganic Arsenic (EPA, 2014).

EPRI is a nonprofit corporation organized under the laws of the District of Columbia Nonprofit Corporation Act and recognized as a tax exempt organization under Section 501(c)(3) of the U.S. Internal Revenue Code of 1986, as amended, and acts in furtherance of its public benefit mission. EPRI was established in 1972 and has principal offices and laboratories located in Palo Alto, California; Charlotte, North Carolina; Knoxville, Tennessee; and Lenox, Massachusetts. EPRI conducts research and development relating to the generation, delivery and use of electricity for the benefit of the public. An independent, nonprofit organization, EPRI brings together its scientists and engineers as well as experts from academia and industry to help address challenges in electricity, including reliability, efficiency, health, safety and the environment. EPRI also provides technology, policy and economic analyses to inform long-range research and development planning, as well as supports research in emerging technologies.

Overall, the Agency is to be commended for its efforts to develop methods for organizing and evaluating the extensive database associated with the health effects of inorganic arsenic. It is a nontrivial task to integrate such a large volume of data in a comprehensible and comprehensive manner.

Nevertheless, EPRI has identified a number of key issues with the Draft Materials which we believe need to be addressed prior to assessment development. More specifically, the organization of the document and the detail provided make it difficult to determine some of the methods applied, as well as criteria employed for decisions regarding inclusion or exclusion of certain peer-reviewed publications. The net effect of these issues is that it not only decreases the transparency of the approach, but could also potentially skew the literature considered in the IRIS assessment and the conclusions drawn from that assessment. Our specific comments on the document, organized by chapter, are provided below; also included are comments related to Science Issue #6 (Mode of action and adverse outcome pathways). Finally, we have identified typographical and other minor errors; we have outlined these at the end of this set of comments for your consideration.

**Our overarching comments include:**

1. Regarding Science Issue #6 (Mode of action and adverse outcome pathways), recent EPRI-supported research supports the conclusion that a non-linear dose-response relationship is operative at low arsenic exposures. A number of EPRI-supported studies do not appear in the Draft Materials (see pages 6-8 for complete citations), including Broeckaert et al. (1997), Broeckaert et al. (1999), Buchet et al. (1997), Clewell et al. (2007), Clewell et al. (2011), Crecelius and Yager (2011), Gentry et al. (2005), Gonsebatt et al. (1997), Kedderis et al. (2006), Kenyon et al. (2008), Mann et al. (1996a), Mann et al. (1996b), Schoof and Yager (2007), Tice et al. (1997), Wiencke and Yager (1992), Wiencke et al. (1997), Williams et al. (2006), Yager et al. (1997), Yager and Wiencke (1993), and Yager

- and Wiencke (1997). A recently published paper by Gentry et al. (2014) should also be included.
2. The Draft Materials do not align with all the recommendations made by National Research Council (2013), including lack of specific criteria to determine sufficient, suggestive, or inadequate evidence for causality; consideration of study quality in a systematic manner; and lack of specifics regarding the mode of action analysis. We recommend that the Agency carefully review the NRC's recommendations and modify the document accordingly.
  3. The Draft Materials do not contain sufficient detail to enable a third party to recreate the literature search and results, including clear criteria for inclusion and exclusion of studies. We note that a number of studies are missing from the Draft Materials, with no explanations as to why they were excluded. Since the ultimate selection of data for inclusion and consideration in the IRIS assessment is critical to the objective and unbiased evaluation of inorganic arsenic, this is a significant deficiency in the Draft Materials.
  4. While the "risk of bias" evaluation adds value to the assessment, other study characteristics – such as study design and quality – should be considered as well.
  5. It is unclear if or how the approach for identifying appropriate literature for the hazard identification will be used to identify studies to inform the dose-response assessment of inorganic arsenic.

#### **COMMENTS ON SCIENCE ISSUE #6: MODE OF ACTION AND ADVERSE OUTCOME PATHWAYS**

There is a large body of EPRI-supported literature, dating back to 1992, which reports on various issues related to arsenic health effects, including epidemiology cross-sectional studies of both oral and inhalation arsenic exposure, toxicology studies addressing specific organ effects by oral and respiratory routes, arsenic mammalian kinetics and metabolism, and significant mode of action studies. The most recent work focused on mode of action has pointed to a non-linear dose-response relationship at low arsenic exposures. We note that the majority of the EPRI-supported research articles are not included in the reference list in the Draft Materials. It is not clear why these papers have been excluded from consideration (although some are recently published, most were published prior to 2014), nor where in the literature review the exclusion occurred. The missing references are provided at the end of this section.

#### ***Overview of Recent EPRI Mode of Action Research on Arsenic***

In the National Research Council report (NRC, 2013) that describes desirable aspects of the conduct of a dose-response assessment for inorganic arsenic, the committee stated that epidemiology studies would form the basis of a risk assessment for arsenic. The committee also remarked that mode of action data should be used, to the extent possible, to extrapolate below the observed range for epidemiological studies to inform the shape of the dose-response curve. EPRI has supported a series of studies focused on mode of action to understand the development of bladder effects and cancer following exposure to

inorganic arsenic and to provide data to inform the dose-response curve (Gentry et al., 2010; Clewell et al., 2011; Yager et al. 2013). More recently, published EPRI-supported work addresses integration of mode of action data combined with bladder cancer epidemiology studies to inform the dose-response curve in the low dose region following exposure to inorganic arsenic (Gentry et al., 2014a). Specifically, integration of these results including values for both pharmacokinetic and pharmacodynamic variability suggests that arsenic exposures in the range of 7 – 43 ppb in drinking water are extremely unlikely to elicit changes leading to key events in the development of cancer or noncancer effects in bladder tissue (Gentry et al., 2014b). These findings are consistent with the lack of evidence for bladder cancer following chronic ingestion of arsenic water concentrations < 100 ppb in epidemiological studies.

A brief description of foregoing key studies follows: Gentry et al. (2010) performed a comprehensive literature search on studies containing quantitative dose-response information in gene or protein expression changes following exposure to inorganic arsenite or arsenate in either *in vivo* or *in vitro* systems. For each gene or protein evaluated, the lowest concentration associated with a significant increase or decrease in expression was identified and a comparison of the changes by functional category and dose was conducted. A transition in expression response related to exposure concentration was observed across an array of mammalian cell types. Responses at concentrations  $\leq 0.1 \mu\text{M}$  inorganic arsenic indicated adaptive responses while those studies in which exposures were between  $0.1 \mu\text{M}$  and  $10 \mu\text{M}$  resulted in responses related to oxidative stress, proteotoxicity, inflammation, proliferative signaling, cell cycle G2/M checkpoint control, inhibition of DNA repair, and apoptosis/survival signaling. At *in vitro* exposures  $> 10 \mu\text{M}$ , changes in apoptotic genes prevailed. Immortalized and primary cells responded similarly, however, gene expression in tumor-derived cell lines appeared to be altered due to inactivation or over expression of key genes.

Subsequently, in an *in vivo* drinking water study conducted in mice (Clewell et al. 2011), significant changes in the expression of genes associated with similar pathways to those observed in *in vitro* studies were noted in mouse bladder cells following 1 or 12 weeks of exposure. The changes in gene expression were bimodal in nature, with substantial changes in expression following exposure to the lowest concentration (0.5 mg As/L) and the two highest concentrations (10 and 50 mg As/L), but few significant changes observed following exposure to 2 mg As/L. This bimodal concentration-response likely reflects a concentration-dependent transition in the effects of arsenic on the mouse urinary bladder. Further support for a transition is provided by a minimal overlap in the genes affected at the low and high drinking water concentrations at either time-point, as well as striking differences in the pathways affected at the low and high concentrations. The mouse study provided additional evidence for a transition in gene expression comparable to that noted in the review of the *in vitro* data in primary cells (Gentry et al. 2010), with a transition or threshold concentration on the order of  $0.1 \mu\text{M}$ .

Substantiation of the  $0.1 \mu\text{M}$  transition value was seen in results from an *in vitro* study conducted in primary human uroepithelial cells from 15 normal individuals exposed to arsenic and its methylated metabolites (Yager et al., 2013). Analyses of gene expression

changes were conducted following incubation for 24 hours with a mixture of arsenite and its metabolites representative of the mixture expected to be present in the human bladder based on evaluation of human urine samples. Significant changes in gene expression for the most common genes affected across individuals were observed at concentrations in the range of approximately 0.1 to 1.0  $\mu\text{M}$  arsenic for both trivalent and pentavalent arsenic mixtures. These results are consistent with the changes noted in the review of studies of primary cells *in vitro*, as well as in mouse bladder cells *in vivo*, providing additional evidence of a threshold or transition concentration critical to the toxicity of arsenic compounds. The most common pathways affected in individuals (Yager et al. 2013), in agreement with the integrated *in vitro* data (Gentry et al. 2010) and *in vivo* mouse data (Clewett et al. 2011), were genes related to oxidative stress response (i.e., heme oxygenase-1 (HMOX1), thioredoxin reductase, thioredoxin, metallothionein regulation); protein folding (FKBP5), DNA damage sensing (DDB2), cell adhesion, growth regulation (LGALS8) and immune response (THBD).

Benchmark dose (BMD) analyses on gene expression results in primary human bladder cells showed benchmark dose lower confidence limits (BMDLs) in the range of 0.09–0.58  $\mu\text{M}$  for total arsenic in trivalent arsenical mixtures; and 0.35–1.7  $\mu\text{M}$  for total arsenic in pentavalent mixtures. BMDs and BMDLs varied by an approximate factor of three across individuals. No observed effect levels (NOELs) ranged from 0.18  $\mu\text{M}$  – 1.8  $\mu\text{M}$  total arsenic concentration for these same genes.

#### ***Other Arsenic-Related EPRI Research***

***Mode of Action Studies.*** Earlier *in vitro* mode of action studies supported by EPRI include those addressing potential mechanisms of co-mutagenicity and inhibition of DNA repair (Wiencke and Yager, 1992; Yager and Wiencke, 1993; Wiencke, et al., 1997; Yager and Wiencke, 1997). Observed clastogenic activity of arsenic and lack of induction of point mutations at single gene loci suggest the possibility of a nonlinear dose-response.

***PBPK Models.*** Development of the first published human arsenic PBPK model was supported by EPRI (Mann et al., 1996a; Mann et al., 1996b). A PBPK mouse model was developed (Gentry et al., 2004); studies to provide additional information on arsenic methylation kinetics (Kedderis et al, 2006), *in vivo* distribution and excretion in B6C3F1 mice (Tice et al, 1997; Kenyon et al., 2008); and mouse tissue dosimetry (Gentry et al., 2005) were also conducted.

***Arsenic in Coal Fly Ash.*** *In vivo* rodent respiratory tract investigations conducted to examine retention and inflammatory lung effects in response to exposure to either arsenic-containing coal fly ash or arsenic-containing copper smelter dust revealed substantial retention and inflammatory response to copper smelter dust exposure relative to coal fly ash (Broeckaert et al., 1997; Buchet et al., 1997; Broeckaert et al, 1999). An occupational study of arsenic coal fly ash exposure that measured individual breathing zone particle size distribution and urinary excretion showed relatively low urinary arsenic excretion concentration relative to the mean arsenic Threshold Limit Value due to

deposition of predominantly large particles in the nasopharyngeal region (Yager et al., 1997).

**Method Development.** EPRI supported an international round-robin laboratory study to provide information on reproducibility of analytical methods for speciation of arsenic in human urine (Crecelius and Yager, 1997). A summary of progress to date on development of a dose-response assessment for arsenic was also supported (Clewell et al., 2007).

**Human Biomonitoring.** Arsenic drinking water exposure, urinary excretion, arsenic-specific skin lesions and cytogenetic endpoints were studied in two villages with differing arsenic drinking water concentrations (20 ppb and 400 ppb). Those most highly exposed tended to have increased skin effects as well as higher chromosomal aberrations in peripheral lymphocytes (Gonsebatt et al., 1997).

**Arsenic in Food Fish.** Review studies were undertaken to estimate total and speciated arsenic in commonly consumed fish and seafood (Schoof and Yager, 2007) and to address arsenic bioaccumulation in freshwater fishes (Williams et al., 2006).

#### **Missing EPRI-Supported References**

- Broeckaert, F., Buchet, J.P., Huaux, F., Lardot, C., Lison, D., Yager, J.W. 1997. Reduction of the *ex vivo* production of tumor necrosis factor alpha by alveolar phagocytes after administration of coal fly ash and copper smelter dust. *J. Toxicol. Environ. Health* 51:189-202.
- Broeckaert, F., Buchet, J.P., Delos, M., Yager, J.W., Lison, D. 1999. Coal fly ash- and copper smelter dust-induced modulation of *ex vivo* production of tumor necrosis factor-alpha by murine macrophages: effects of metals and overload. *J. Toxicol. Environ. Health Part A*. 56 (5): 343-360.
- Buchet, J.P., Lauwerys, R., Fabries, J.F., Yager, J.W. 1997. Factors affecting the retention in hamster lung of arsenic present in fly ash and copper smelter dust, In: *Arsenic: Exposure and Health Effects*, C.O. Abernathy, R.L. Calderon, W.R. Chappell (Eds), Chapman & Hall, N.Y., p. 272-282.
- Clewell, H.J., Thomas, R.S., Gentry, P.R., Crump, K.S., Kenyon, E.M., El-Masri, H.A., Yager, J.W. 2007. Research toward the development of a biologically based dose response assessment for inorganic arsenic carcinogenicity: A progress report. *Toxicol. Appl. Pharmacol.* 222: 388-398.
- Clewell, H.J., Thomas, R.S., Kenyon, E.M., Hughes, M.F., Adair, B.M., Gentry, P.R., Yager, J.W. 2011. Concentration- and time-dependent genomic changes in the mouse urinary bladder following exposure to arsenate in drinking water for up to twelve weeks. *Toxicol. Sci.* 123(2):421-32.
- Crecelius, E., Yager, J.W. 1997. Interlaboratory comparison of analytical methods for arsenic speciation in human urine. *Environ. Health Perspect.* 105 (6): 650-653.

- Gentry, P.R., Clewell, H.J., Greene, T.B., Franzen, A.C., Yager, J.W. 2014a. The impact of recent advances in research on arsenic cancer risk assessment. *Regul. Toxicol. Pharmacol.* 69(1):91-104.
- Gentry, P.R., Yager, J.W., Clewell, R.A., Clewell, H.J. III. 2014b. Use of mode of action data to inform a dose-response assessment for bladder cancer following exposure to inorganic arsenic. In press, *Toxicol. In Vitro*.
- Gentry, P.R., Covington, T.R., Lawrence, G., McDonald, T., Snow, E.T., Germolec, D., Moser, G., Yager, J.W., Clewell, H.J. 3rd. 2005. Comparison of tissue dosimetry in the mouse following chronic exposure to arsenic compounds. *J. Toxicol. Environ. Health Part A* 68(5):329-351.
- Gonsebatt, M.E., Vega, L., Salazar, A.M., Montero, R., Guzman, P., Blas, J., Del Razo, L.M., Garcia-Vargas, G., Albores, A., Cebrian, M.E., Kelsh, M., Ostrosky-Wegman, P. 1997. Cytogenetic effects in human exposure to arsenic. *Mutat. Res.* 386(3): 219-28.
- Kedderis, G.L., Elmore, A.R., Crecelius, E.A., Yager, J.W., Goldsworthy, T.L. 2006. Kinetics of arsenic methylation by freshly isolated B6C3F1 mouse hepatocytes. *Chem. Biol. Interact.* 161(2):139-145.
- Kenyon, E.M., Hughes, M.F., Adair, B.M., Highfill, J.H., Crecelius, E.A., Clewell, H.J., Yager, J.W. 2008. Tissue distribution and urinary excretion of inorganic arsenic and its methylated metabolites in C57BL6 mice following subchronic exposure to arsenate in drinking water. *Toxicol. Appl. Pharmacol.* 232(3):448-55.
- Mann, S., Droz, P.O., Vahter, M. 1996. A physiologically based pharmacokinetic model for arsenic exposure. I. Development in hamsters and rabbits. *Toxicol. Appl. Pharmacol.* 137(1):8-22.
- Mann, S., Droz, P.O., Vahter, M. 1996. A physiologically based pharmacokinetic model for arsenic exposure. II. Validation and application in humans. *Toxicol. Appl. Pharmacol.* 140(2): 471-86.
- Schoof, R.A., Yager, J.W. 2007. Variation of total and speciated arsenic in commonly consumed fish and seafood. *Hum. Ecol. Risk Assess.* 13:946-965.
- Tice, R.R., Yager, J.W., Andrews, P., Crecelius, E. 1997. Effect of hepatic methyl donor status on urinary excretion and DNA damage in male B6C3F1 mice treated with sodium arsenite. *Mutat. Res.* 386 (3): 315-334.
- Wiencke, J.K., Yager, J.W. 1992. Specificity of arsenite in potentiating cytogenetic damage induced by the DNA crosslinking agent diepoxybutane. *Environ Molec. Mutagen* 19(3): 195-200.
- Wiencke, J.K., Yager, J.W., Varkonyi, A., Hultner, M., Lutze, L.H. 1997. Study of arsenic mutagenesis using the plasmid shuttle vector pZ189 propagated in DNA repair proficient human cells. *Mutat. Res.* 386 (3): 335-344.
- Williams, L., Schoof, R.A., Yager, J.W., Goodrich-Mahoney, J.W. 2006. Arsenic bioaccumulation in freshwater fishes. *Hum. Ecol. Risk Assess.* 12:904-923.

- Yager, J.W., Hicks, J.B., Fabianova, E. 1997. Airborne arsenic and urinary excretion of urinary metabolites during boiler cleaning operations in a Slovak coal-fired power plant. *Environ. Health Perspect.* 105 (8): 836-842.
- Yager, J.W., Wiencke, J.K. 1993. Enhancement of chromosomal damage by arsenic: implications for mechanism. *Environ. Health Perspect.* 101 (Suppl. 3): 79-82.
- Yager, J.W., Wiencke, J.K. 1997. Inhibition of poly (ADP-ribose) polymerase by arsenite, *Mutat. Res.* 386: 345-351.

## **CHAPTER 1: ASSESSMENT DEVELOPMENT PLAN FOR THE TOXICOLOGICAL REVIEW OF INORGANIC ARSENIC**

According to the Draft Materials, the Agency is committed to developing the inorganic arsenic toxicological review in a transparent process, with transparency being defined by USEPA as “sufficient information will be available to understand the scientific rationale behind decisions, as well as reproduce methods used to identify and evaluate data.” (page 1-12). However, a well-defined protocol for all steps of the process has not been provided and therefore is inconsistent with the recommendations of the National Research Council (NRC, 2013), which state:

*“A priori decisions and a predefined protocol are critical during the systematic review process (Berlin and Colditz 1999; Dickersin 2002); the protocol should describe the following steps: the research question, the search strategy and data sources, the study inclusion and exclusion criteria, the data to be abstracted and derived from the original studies (such as sample size, exposure and outcome assessment methods, and confounders evaluated), the criteria and methods for pooling effect estimates and measures of variability among studies. Systematic reviews and meta-analyses need to be replicable; other investigators following the same steps should be able to identify the same articles, abstract the same data, and reach similar conclusions.”*

At each step of the process for identifying studies for inclusion in the toxicological review, a detailed set of criteria is needed (NRC, 2013; Rooney, 2013). For example, if decisions are made to include or exclude any studies, there should be very detailed criteria indicating why studies were included or excluded. The criteria for each step should be described in such a way that an outside reviewer could use them to replicate the results of the literature search and review. There are several areas within the Assessment Development Plan where this level of detail is lacking. In addition, the Draft Materials suggest that the details needed for transparency may not be possible. For example, Section 1.3.3 on transparency states: “*When possible*, the toxicological review will present options for key decision points and provide rationale for choosing a particular option” (page 1-12). It is difficult to comprehend when and why this would not be possible. Overall, the lack of a fully transparent process may lead to exclusion of relevant data from consideration in the IRIS toxicological assessment.

Specific examples of areas of concern regarding transparency and other related issues are listed below.

### **Identifying Relevant Literature**

*Comment: The approach does not indicate specifically which criteria will be used to include or exclude studies at each step of the process of identifying relevant literature.*

- In Table 1-5 (page 1-33), no specific criteria are provided to determine sufficient, suggestive, or inadequate evidence for causality. For example, evidence for a causal relationship is stated to include: “controlled human exposure studies that demonstrate consistent effects; or observational studies that cannot be explained by plausible alternatives or are supported by other lines of evidence.” This definition is very subjective for a systematic review. It is unclear if statistical methods are to be used to determine causality in epidemiological or animal studies. Based on the level of detail presented, it would not be possible for a reviewer to replicate the decisions applied in the determination of the evidence.
- In Figure 1.4 (page 1-47), at each level at which studies were excluded the criteria used to make decisions is not provided. The figure indicates “not included in hazard identification”, “not included in evidence table”, “suggestive”, “inadequate”, “not likely”. However, there is no systematic list of criteria provided for each step to determine inclusion and exclusion.
- In Section 1.5.5.1 (page 1-48) the text states that ... “the remaining references will be grouped using natural language processing. A computer algorithm groups references into clusters based on similarity in the title and abstract.” An expanded definition of “natural language processing” is needed. In addition, it is unclear what software would be needed to duplicate this processing. As approximately 28,000 citations were removed from consideration with this step of the process, additional information on the exclusion criteria is needed, as well as additional information on how the data were clustered.

### **Risk of Bias Approach**

*Comment: The “risk of bias” approach applied should be documented more comprehensively.*

EPA has chosen to heavily rely upon a “risk of bias” approach developed by the Office of Health Assessment and Translation (OHAT) at the National Institute of Environmental Health Sciences (NIEHS) in guiding the determination of the evidence for health effects from inorganic arsenic. EPA notes in Section 2.6.1 that the OHAT approach is in draft form and that “A version of this draft protocol (which continues to evolve) has been adopted for use in this assessment of inorganic arsenic because it provides a unified approach for evaluating risk of bias from animal and epidemiology studies.” Other approaches for assessing bias are available (e.g., Viswanathan et al., 2012). Standard

protocols for systematic review and synthesis of epidemiological clinical intervention research evidence to inform decisions have been available for some time (Cochrane, 2008). The approach applied in the Draft Materials should be very clear. One suggestion would be to include it as an Appendix, so that there is no question of the process (and version) that is being followed, particularly in light of it being a dynamic document.

In regard to documenting the approach applied, it is unclear if the modifications made to the OHAT approach for application to inorganic arsenic will impact the goal of the toxicological review and the ability to identify the primary studies relevant for understanding the evidence for hazard identification. Further consideration is also needed to determine if this approach, which is focused on hazard identification, assists in the identification of studies needed for dose-response analysis.

- For the epidemiological data, 6 “risk of bias” questions were chosen to be most informative and for the animal toxicological data, 2 questions were selected. OHAT recommends 10 questions for epidemiological studies and 14 for animal toxicological studies. It is unclear how these questions were selected, and what the impact could be on the approach to identify primary and secondary studies.
- The second paragraph of Section 1.5.5.4 (page 1-56) states, “Evidence tables will serve as an additional method for presenting and evaluating whether the data are fit-for-purpose (i.e., informing hazard identification for inorganic arsenic). For each health effect domain, a series of specific questions or criteria will be developed to help inform the fit-for-purpose, based upon NRC recommendations (NRC, 2013).” It is unclear what is meant by the term “fit-for-purpose”. It is also unclear as to whether or not these questions have been developed yet, or if they will be part of the next step in the IRIS assessment development. Finally, it is unclear if these additional questions are critical for the identification of dose-response data.

*Comment: Additional documents needed to fully document the process appear to be under development.*

Section 1.5.5.7 (page 1-61) describes an additional document that will be generated and will provide additional details on the identification and evaluation of the literature for hazard identification. As presented, this document will describe the identification of references, the use of natural language processing to group studies, and the categorization of references by title, abstract, and/or full text review. This document may contain some of the information needed to improve the transparency of this process. It is unclear if this document has been developed. This type of information is necessary to understand the process and should not be supplementary material.

*Comment: Risk of bias should not be the only consideration. Study design and quality should also be considered.*

Adequacy of study methods and quality should be considered along with risk of bias for determining which are considered the primary studies, especially for animal and *in vitro*

studies. Relevant studies may otherwise be excluded that might contain important information regarding the causal relationship between inorganic arsenic exposure and outcomes.

## **CHAPTER 2: LITERATURE SEARCH STRATEGY AND SYSTEMATIC REVIEW FOR DEVELOPMENT OF THE TOXICOLOGICAL REVIEW OF INORGANIC ARSENIC**

*Comment: Insufficient detail is presented to recreate the literature search and results of the systematic review.*

- The information presented in Figure 2-1 (page 2-2) or the text in Chapter 2 is inadequate for the reviewer to determine why studies were excluded at each step of the literature search and review process. While some of this information may be presented in a very general format in Chapter 1, specific inclusion and exclusion criteria developed for the literature review process should be provided. At each step indicated in Figure 2-1 where references were eliminated, there should be a detailed set of criteria used to determine inclusion or exclusion. Some of the criteria are clear (e.g., foreign language), but many are not (e.g., not found in health effects cluster, supporting study, etc.). Overall, additional detail should be provided regarding the culling of the initial 43,802 references to 530.
- The number of citations presented in Figure 2-1 (page 2-2) at each step of the literature review process, does not match the values presented in the HERO data base at [http://hero.epa.gov/index.cfm?action=litflow.viewProject&project\\_id=2211](http://hero.epa.gov/index.cfm?action=litflow.viewProject&project_id=2211).
- It is unclear why the search strings presented in Table 2-1 (page 2-2) contain both inorganic and organic forms of arsenic when this review focuses on the toxicological effects of inorganic arsenic. It is of interest whether this was to capture data regarding arsenic metabolites. It is also unclear why arsenic trioxide, a form of inorganic arsenic, was specifically excluded in the literature search strings provided (NOT “arsenic trioxide”).
- Section 2.3 (page 2-3) discusses how references were clustered into groups based on language similarity using OmniViz reference visualization software. The Draft Materials indicate that “seed” studies were used to identify relevant studies. For transparency, these “seed” studies or the criteria for their selection should be provided. Because approximately 24,000 references were excluded during this step of the literature search strategy, a more in-depth discussion of this software and how it works is warranted. Specifically:
  - No criteria were given to determine the inclusion or exclusion of studies to determine the 900 “seed” studies used to identify relevant hazard identification data.

- No criteria were given to determine the inclusion or exclusion of studies to determine the 400 “seed” studies used to identify relevant mode of action data.
- All parameters used in the OmniViz software should be reported.
- Section 2.4 (page 2-5) states that categorization of the references and all following steps were performed in a database. It is unclear as to whether Dragon the database was used to facilitate data management. Dragon is mentioned in following sections but not specifically here. It is not clear how decisions were documented and consistency maintained throughout the processes, or if any quality control procedures were in place during the literature search and review process, and if so, what types. Multiple sections in the Draft Materials mention multiple reviewers (Section 1.5.5.2.1 [page 1-51], Section 2.4 [page 2-5]) with a third reviewer brought in for discrepancies (Section 2.4.1 [page 2-5]) or the reviewers resolving discrepancies between ratings (Section 1.5.5.2.2 [page 1-5]). A description of the quality control measures implemented at each step of the literature search and review process is needed, including which software was used to categorize data.
- One of the search engines used to identify literature was the Web of Science. This search engine is not publicly available and requires a significant fee to use. The lack of free access of this search engine to the general public will limit the ability of all reviewers to duplicate the literature search process, thereby decreasing the transparency of the results.
- In Section 2.4.1 the document indicates that 653 epidemiology studies and 99 animal studies were identified based on title and abstract categorization. It is not clear whether these are independent studies or multiple publications on the same cohort or animal study.
  - Epidemiology data should be identified by the cohort with all publications resulting from that cohort listed together. Counting of multiple “studies” based on the same cohort should not be done.
  - Animal data should be identified by the actual animal experiment, not by the various publications on the study. Counting evidence from one study multiple times will falsely give that study more weight.

*Comment: A quality assurance check of the results of the literature search strategy is needed to ensure that critical primary literature has been identified. Otherwise, important studies may be excluded.*

- An initial review of recent review articles suggests that critical primary literature has been excluded using the current literature search strategy.
  - Using a search term provided in Table 2-1 (page 2-4), a brief literature search was conducted in PubMed and a comparison of the search results to the epidemiological literature presented in Chapter 3 was performed. Citations identified using the search terms provided in the Draft Materials were not

provided in Chapter 3 of the Draft Materials. Because of the lack of clear exclusion criteria, it is unclear why these studies were excluded.

- The epidemiological literature provided in Chapter 3 of the Draft Materials was also compared to citations in a recent review focused on health effects reported in children exposed to water containing inorganic arsenic (Majumdar and Mazumder, 2012). Four primary studies (Guha et al., 1998; Watanabe et al., 2007; Guo et al., 2001; Ahsan et al., 2000) identified in that review were not included in the Draft Materials, and it is not clear why they were excluded.
- A cross-reference of the primary literature identified in Gentry et al. (2010) was performed against the mode of action literature (Chapters 8-10) in the Draft Materials. Only 2 studies of the 35 primary studies listed as important to the characterization of the dose-response relationship by Gentry et al. (2010) were referenced in the Draft Materials. It is not clear why these mode of action studies were excluded.

*Comment: The literature search strategy does not appear to be consistent with comments from the NRC (2013).*

- The NRC states “Exposure to metabolites will be considered only in mode-of-action analysis.” Literature search strategies outlined in Table 2-1 (page 2-4) include metabolite keywords. It is not clear whether metabolite studies in the hazard identification were excluded for consideration in this section.
- The NRC states “Literature search and evaluation – Systematic review principles will be used to evaluate the scientific literature on inorganic arsenic, and studies will be judged according to defined criteria and such factors as bias and study quality.” The Draft Materials consider bias, but do not consider study quality in a systematic manner.

#### **CHAPTERS 3, 4, AND 5: SUMMARY OF LITERATURE IDENTIFIED/RISK OF BIAS/EVIDENCE TABLES – EPIDEMIOLOGICAL STUDIES**

*Comment: Study design is equally important as bias assessment and should be considered systematically.*

Basic study design is a very important factor in any particular epidemiology study since the primary purpose of evaluating these studies is to provide sound information with regard to the central critical issues of exposure-response and causality. Study design should therefore be considered along with risk of bias. Basic epidemiological methods emphasize that the strongest study design for assessing causality is the **cohort study**; this design also provides the most direct measurement of risk (WHO, 2006). The terms “prospective cohort study” and “retrospective cohort study” refer to the timing of data collection and not to the relationship between exposure and effect. Therefore, for each set of Tables in Sections 3, 4, and 5, cohort studies should be grouped together and evaluated as the strongest evidence in consideration for assessment of hazard identification and exposure-response. **Case-control** and **nested case-control** study designs are next in

strength to assess associations since they are longitudinal in nature (and data from the past may be collected or data collection may continue from the present forward in time). Finally, for **cross-sectional** study design, measurement of exposure and effect are made at the same time; thus, interpretation of association relative to causality is difficult since it may not be clear whether exposure precedes or follows the outcome. If it is known that exposure data do represent exposure before any effect occurred, then data from such a cross-sectional study may be assessed as if it were a cohort study. We recommend that studies for each category of health effect be rearranged to list cohort designs first in publication-date order, then case-control studies, and finally (and separately), cross-sectional studies in order of importance to the task/health effect, rather than listing them in alphabetical order by first author's last name.

*Comment: Epidemiology tables should be ordered by hierarchical disease category as recommended by NRC.*

NRC (2013) recommends a three-tiered approach to examination of the epidemiology literature based on a hierarchy of disease outcomes (Box 2, p. 5). The tables in Chapter 3, as well as the Epidemiology Evidence Tables (Chapter 5), should be listed in the recommended order by disease category and to be expressed according to ICD classification (see next Comment).

*Comment: Diseases described in epidemiology studies should be organized by international classification of disease (ICD) categories for accurate comparisons across studies.*

A number of individual epidemiology studies describe multiple diseases or adverse health outcomes. This often leads to a single study being listed multiple times in current health outcome tables (e.g., Chapter 3). Further, the recording of health outcomes in tables is highly inconsistent within one disease category (e.g., Table 3.12, Summary of Epidemiology Studies for Hazard Identification for Cardiovascular Disease). The ICD has been developed by the World Health Organization over many years and is periodically updated. Although ICD-10 has been available since 1994, currently the ICD-9 and a clinical modification, ICD-9-CM, are used in the United States (Centers for Disease Control and Prevention, 2014). Whichever ICD classification scheme is used should be thoroughly documented and applied to the disease descriptions in epidemiology studies by an expert in ICD coding procedures. The process should then be fully described in table footnotes and accompanying text as to the exact classification category having been assigned to the described disease or adverse health outcomes as reported in individual studies.

*Comment: Improved transparency is needed in derivation and application of bias evaluation criteria.*

- Risk of bias is one consideration in assessing the veracity of findings in epidemiology studies; however, study design supersedes schemes to assess risk of bias. Further, in Table 1-10 (page 1-70), OHAT Questions 1 and 2 are not appropriate for

observational environmental epidemiology studies, e.g., Q. 1 “Was administered dose or exposure level adequately randomized?”

- Section 4. *Summary of Risk of Bias Evaluations for Inorganic Arsenic Epidemiologic Studies*, Tables 4.1 – 4.14: Neither OHAT criteria or the description of the modified OHAT criteria in the Draft Materials are directly comparable with the Risk of Bias table headings. First, as described in OHAT, the sole key questions to be applied to epidemiology studies ranking each characteristic qualitatively (++ , + , - , --) are:
  - *Selection Bias*:
    - Were the comparison groups appropriate?
    - Did the study design or analysis account for important confounding and modifying variables?
  - *Performance Bias*:
    - Did researchers adjust or control for other exposures that are anticipated to bias results?
  - *Detection Bias*:
    - Can we be confident in the exposure characterization?
    - Can we be confident in the outcome assessment?
  - *Other*:
    - Were there any potential threats to internal validity (e.g., inappropriate statistical methods)?
- In addition to the above criteria as listed in OHAT, additional table headings (Tables 4.1 -4.14) include: Confounding: “Unintended Exposure”, Attrition (attrition/exclusion): “Missing Outcome Data”, Detection: “Blinding (Outcome Assessment)”, SRB (selective reporting bias): “Outcome Reporting”. The OHAT approach is an improvement over earlier attempts to categorize arsenic epidemiology studies; however, the criteria remain principally subjective. The addition of another four criteria does not make it more transparent whether or not a particular study is severely biased since it is known that all epidemiology studies by their observational nature will contain some form(s) of bias. Such study bias is virtually unavoidable, but can be qualitatively assessed to some degree for individual studies. Addition of more detailed criteria as shown may lend a false sense of assurance that adding more criteria somehow increases study validity.
- As mentioned above, study design supersedes evaluation of bias, thus bias evaluation needs to be simplified and placed secondarily (using original OHAT criteria or modified criteria as stated above) after consideration and ranking of basic study design and its eventual relevance to assessment of exposure-response and causality. Although Table 1-10 provides good descriptions of criteria for such questions as “Were the comparison groups appropriate?” the excruciatingly detailed and highly technical approach to address evaluation of bias criteria do not lend themselves to increased transparency. Evaluation of bias criteria should be simplified to questions appropriate to these study designs. To approach the evaluation of bias by more complex means does little to improve transparency of the analysis.

*Comment: Specific evidence table construction for multiple studies conducted on the same or overlapping cohorts in a specific geographic location is needed in order to expedite and clarify the future weight of evidence evaluation. This will help to avoid consideration of related studies as truly independent.*

Since a preponderance of arsenic health effects data arise from just a few geographic locations globally, it is important that EPA set up initial data tables to facilitate future adjustments to weight-of-evidence considerations when results demonstrating health effects arise from studies conducted on identical or nearly identical population cohorts in similar areas. For a number of authors and locations, multiple studies have been published that were conducted on the same cohort or cohort sub-set and within the same time period within a defined geographic area (e.g., specific areas of Bangladesh or Taiwan). As a consequence, results from these studies for any given health outcome do not constitute truly independent information so that each study contributes a fraction of evidence in a weight-of-evidence analysis. It would help if multiple health outcome study results from the same or nearly the same cohort were placed into one table for each defined outcome, with citations for each publication indicated in the table and listed in table footnotes.

*Comment: Epidemiology study designs are not consistently categorized.*

Section 2.6.2.1 (page 2-12) *Prioritization and Assessing Risk of Bias in Epidemiology Studies*: Here, definitions of epidemiologic study design should be precisely described and then used consistently throughout the document. Initially, three types of designs – case-control, cohort, and cross-sectional studies – were listed as those solely to be included in the full risk of bias evaluation and the evidence tables. Ecological, case series, and case reports were to be excluded. Later in the document, however, (Section 3.1.2 [page 3-6]) various sub-types of epidemiological study designs are named, such as “case-cohort”, “case-control (nested)”, etc. A very clear definition of each type of study design attributed to each published study should be determined at the outset, and then these terms should be carefully and consistently employed throughout the analysis.

*Comment: Epidemiology study tables contain inconsistent/undefined headings and entries.*

- Epidemiology Summary Tables, Sections 3.1.1 – 3.1.16: Table headings should be consistent, and types of studies should be consistently listed within their defined category. The “Other” category should be defined in a footnote with an all-inclusive list of the study design types included in this category. For example, case reports, case series and perhaps case-cohort (the former needs to be clearly defined) studies could all be placed in the “Other” category.
- Tables 4.1 – 4.14 should be presented in the same order of health effects categories as Tables 3.1.1 – 3.1.15 and Tables 5.1 – 5.16. The “Other” category of health effects should be clearly explained.

- In Table 3.1.12, *Summary of Epidemiology Studies for Hazard Identification of the Nervous System* (page 3-31), health effects described here overlap (e.g., CNS: function – cognition; CNS: function – behavioral [4 types]) with those listed in Table 3.1.4 *Summary of Epidemiology Studies for Hazard Identification for Developmental Effects including Neurodevelopmental* health effects description (e.g., Table 3.1.4, Hamadani et al. (2010) Health effect: CNS-function-cognition (4 types), etc.). It is not clear whether studies cited in Table 3.1.4 are studies exclusively of younger ages and, if so, what are the cut-off ages that would categorize a study into either Table 3.1.12 or Table 3.1.4 given the similar health endpoints being measured? Is there overlap such that the same study could be cited in both tables? Strict ICD coding of health endpoints will likely mitigate many of these concerns.
- One health outcome category – cardiovascular disease (CVD) – was randomly selected to examine the concordance between Table 3.1.2 (*Summary of Epidemiology Studies for Hazard Identification for Cardiovascular Disease*) and Table 4.9 (*Risk of Bias Overview – Cardiovascular Disease*). Approximately 97 studies are listed in the table in Section 3.1.2 (page 3-5) (not counting duplicate entries due to a number of different CVD endpoints determined from the same study). However, 181 total studies are shown in the corresponding figure in Section 3.1.2 (page 3-5). It is not clear whether this number reflects the total number of studies cited or reflects the number of different CVD endpoints derived from those studies. Table 4.9 (*Risk of Bias Overview – Cardiovascular Disease*) lists 73 individual studies; again this number is inconsistent with the approximately 97 CVD studies listed in the table in Section 3.1.2. Detailed explanations for these discrepancies should be provided. Of the 73 studies listed in Table 4.9, 32% are cohort studies. As discussed earlier, cohort studies should be placed first in the evaluation prioritization for this health outcome and all others.
- Due to multiple table entries where multiple health outcomes were assessed in one published study, it is difficult to ascertain exactly how many total epidemiology studies were evaluated; however, it appears that approximately 750 studies were identified (Figure 3.1 *Overview of Epidemiology Studies Identified*) of which perhaps as many as 40% are cohort studies. Again, these should be grouped and placed first in order of evaluation by health outcome.
- Throughout the draft document, there is a need for extensive footnotes and documentation to the tables to make transparent the rationale for defining categories and for placing any particular study into a specific category and for uniformity of all tables.

*Comment: Evidence tables need to include risk of bias evaluation to facilitate more objective consideration of the data.*

- In general, the content and structure of Tables 5.1 – 5.16 is very informative. However, evidence tables should first list cohort studies by ascending publication

date, followed by case-control or nested case-control studies, and finally cross-sectional studies.

- The usefulness of the Evidence Tables would be enhanced if results from a simplified bias analysis for each study could be included in the last columns. This analysis would explain the rating in a very few words for each characteristic for each study scored, e.g., “++” (because) . . . or (--) (because) . . . . The last column of the Evidence Table would list each study’s final P (primary) or S (supporting) rating. Characteristics of P and S designation should be described in the text, and a narrative should accompany each Evidence Table explaining in detail the rationale for each study’s bias rating(s) and P/S designation.
- The use of the term “Exposure Surrogate” in Tables 5.1 – 5.16 is unclear. The term “surrogate” refers to a substitute, e.g., “NO<sub>2</sub> is often used a surrogate for traffic-related pollutants”. It doesn’t seem this is the intended use of the term in the Draft Materials; either a different terminology should be used, or the meaning in this context should be made clear. The number of subjects per category is missing for multiple studies in these tables.

#### **CHAPTERS 3, 6, AND 7: SUMMARY OF LITERATURE IDENTIFIED/RISK OF BIAS/EVIDENCE TABLES – TOXICOLOGICAL STUDIES**

- As is the case for the epidemiological studies, it is difficult to ascertain exactly how many total animal studies were evaluated for this section, due to multiple table entries for one published study that assessed multiple health outcomes. In addition, there appear to be multiple publications using the same underlying experimental data. Perhaps the extraction process could provide the dates over which a given experiment was conducted in order to easily determine whether two studies are truly independent.
- There are differences in the way that data were extracted. For example, in Waalkes et al. (2004b; extraction tables on pages 7-17 to 7-18), the male F1 generation adenoma incidences are correctly given as the nominal count or count of all animals with an adenoma, although the publication also lists the counts where animals are counted only in the carcinoma category if they have both an adenoma and carcinoma. However, in Waalkes et al. (2003; extraction tables on page 7-19 to 7-20), incidence of adenomas in the F1 male mice provides a count of only those animals with an adenoma and without a carcinoma even though the nominal incidence rate is provided in the publication in the footnote to the table. Greater care should be taken in the Draft Materials to ensure that data extraction is consistent across studies.
- The tables presented in Chapter 6 should have a key explaining the symbols and color coding. The information in the table is very difficult to interpret.
- As with Chapter 5, the content and structure of Chapter 7 (as provided in Tables 7.1 – 7.3) is very informative. However, four studies listed as primary studies in Chapter 6

are not included in Chapter 7, with no explanation as to why they were excluded. The studies are Nagaraja and Desiraju (1993), Nagymajtenyi et al. (1985), Waalkes et al. (2003), and Tokar et al. (2010b).

- Also in Chapters 5 and 7, it would be helpful to include a simplified bias analysis for each study in the last columns of the Evidence Table to briefly explain the rating e.g., “++” (because). . . . or (--) (because) . . . . The last column of the Evidence Table would list each study’s final P (primary) or S (supporting) rating. Characteristics of P and S designation should be described in the text. A narrative would need to accompany each Evidence Table explaining in detail the rationale for each study’s bias rating(s) and P/S designation.
- In Section 7.1.1 the title of the section is “References for Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental”. However, this is the animal toxicity section. The same is the case for Sections 7.2.1 and 7.3.1. It appears the titles are incorrect.

#### **CHAPTERS 8 AND 9: MODE OF ACTION**

- The information presented in Chapter 8, which details the literature search strategy, review and categorization of the Mode of Action (MOA) data would have been better represented at the end of Chapter 2. It gets lost in detailed information and tables provided in the later chapters of the Draft Materials.
- Section 8.1 (page 8-1) states “The mode of action literature search strategy began with all references from initial arsenic literature search that were not found in the health effects cluster (see Figure 3.1-1).” This figure cannot be located in the document.
- Section 8.1 (page 8-1) discusses how the 24,000 studies that were not in the health effects cluster identified in Chapter 2 were used in the MOA review. These references were also clustered into groups based on language similarity using OmniViz reference visualization software and “seed” studies were used to identify relevant data. For transparency, these “seed” studies or the criteria for their selection should be provided. As stated previously in the comments for Chapter 2, a more in-depth discussion of this software and how it works is warranted. Specifically:
  - No criteria were given to determine the inclusion or exclusion of studies to determine the 900 “seed” studies used to identify relevant hazard identification data.
  - No criteria were given to determine the inclusion or exclusion of studies to determine the 400 “seed” studies used to identify relevant mode of action data.
  - All parameters used in the OmniViz software should be reported.
- In general, Chapter 9 does not provide an outline of how the MOA analysis for inorganic arsenic will proceed. NRC (2013) suggested 5 major steps in the

development of the inorganic arsenic MOA analysis: 1. Provide problem formulation statement; 2. Tabulate adverse outcomes with supporting and conflicting data; 3. Provide pharmacokinetic data throughout the exposure and temporal range for each adverse health outcome and its precursors; 4. List modes of action for each adverse outcome, linking pharmacokinetic and pharmacodynamics information to health outcomes in an exposure and temporal manner; 5. Construct a concordance table to provide strengths and weaknesses of each proposed mode of action for each species, population, and subpopulation. Will this be the general framework used in the mode of action analysis? If so, what methods will be used to identify adverse outcome pathways, will a mode of action analysis be performed for each adverse outcome pathway, and how will pharmacokinetic data be incorporated into the analysis?

- In Chapter 9, several different MOA hypotheses based on recent reviews from different authors are presented for inorganic arsenic. It is unclear how EPA will incorporate the vast amount of MOA data that has been identified in this review with the current hypotheses that are presented by outside authors.
- A review of Chapter 9 indicates there are approximately 90 MOA studies identified by the NRC in the Hazard Identification section of the report. Approximately half of those articles identified by the NRC as MOA studies are not included in the IRIS Draft Materials. It is not clear why these studies would not be included.
- Section 10.5 (Preliminary Data on Effects Mediated by Oxidative Stress) under “key events: gene expression changes” lists Clewell et al. (2011) as a study in human uroepithelial cells published in *Toxicology Letters*. This reference is also listed incorrectly in Chapter 11 (All References). This is an incorrect citation. The correct citation is:
  - Clewell, H.J., Thomas, R.S., Kenyon, E.M., Hughes, M.F., Adair, B.M., Gentry, P.R., Yager, J.W. 2011. Concentration- and time-dependent genomic changes in the mouse urinary bladder following exposure to arsenate in drinking water for up to twelve weeks. *Toxicol. Sci.* 123(2):421-32.

### **TYPOGRAPHICAL AND OTHER MINOR ERRORS**

There are multiple minor errors in the document, including the following:

- The Draft Materials have used a “less than or equal to” symbol ( $\leq$ ) in selected locations in the document, when it is clear from the NRC (2013) report and from the content of the statement that the “greater than or equal to” symbol ( $\geq$ ) is the correct symbol. The use of the incorrect symbol changes the criteria for critical steps in the approach where it is used incorrectly. Examples include:
  - NRC (2013) states on page 5 “Consider meta-analyses if there are at least three or more peer-reviewed studies. For dose-response meta-analysis, studies will need to have characterized at least three or more exposure levels.” The Draft Materials (page 1-4 in Table 1-1 under NRC recommendations) note “Meta-analyses for hazard

identification if  $\leq 3$  peer-reviewed studies; meta-analyses for dose-response if  $\leq 3$  doses tested”.

- Pages 1-83 and 1-84, Table 1-10 (Risk of Bias Questions and Rating Guidelines – Epidemiology Studies Question 12): a ++ and + sign is assigned to “Human Controlled Trial: There is direct or indirect evidence that the test material is confirmed as  $\leq 99\%$  [or 98%] pure (or impurities have been characterized and not considered to be of serious concern), and that the concentration, stability, and homogeneity of stock material and formulation have been verified as appropriate”.
- Page 1-88, Table 1-10 (Risk of Bias Questions and Rating Guidelines – Epidemiology Studies Question 15): a + sign is assigned to “Assessment-specific Clarification: There are study limitations likely to bias the results towards or away from the null, but adequate sample size was available in each cell ( $n \leq 5$ ), OR sample size is small and acknowledged as a potential limitation by study authors, but significant results were still observed.”
- Page 1-95, Table 1-11 (Additional Information for Risk of Bias Determinations for Animal Toxicology Studies Question 12): a ++ sign is assigned to “There is direct or indirect evidence that the test material is confirmed as  $\leq 99\%$  pure (or impurities have been characterized and not considered to be of serious concern), and that the concentration, stability, and homogeneity of stock material and formulation have been verified as appropriate (Note:  $\leq 99\%$  purity value is considered achievable based on current advertised purity from Sigma-Aldrich).”
- While the document indicates that the HERO database provides all relevant information, many of the links lead to cover pages only or do not provide links to the reference document. For example, the link for the IARC Arsenic Monograph leads to cover pages only. A link is available and could be provided to direct the reviewer to the monograph itself.
- There are references in the Draft Materials to sections or materials that do not exist or are incorrect. For example, Section “5.5.2” is referred to on page 1-60 but apparently refers to Section 1.5.5.2, and “Attachment A” is referred to on page 2-11 and appears to be a reference to Section 1.6. On page 1-55 (line 11), Table 1-7 is referenced; however, the relevant table is Table 1-11.
- The presentation of the materials by endpoint across chapters does not follow the same order or are not contained in each chapter. For example,
  - Sections for bladder effects are provided in Chapters 3 (literature identified) and 5 (evidence), but not in Chapter 4 (risk of bias).
  - The order in which Clinical Chemistry and Urinalysis is provided changes from chapter to chapter. It is the third item in Chapter 3, the first item in Chapter 4, and the third item in Chapter 5.

Addressing these organization and editorial comments may lead to greater clarity and transparency in understanding the approaches applied.

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WHO. 2006. Basic Epidemiology, 2<sup>nd</sup> Ed., Bonita R, Beaglehole R, Kjellstrom T. World Health Organization, Geneva, 2006.

**Bohn, Brent**

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**From:** Cowden, John  
**Sent:** Wednesday, June 11, 2014 11:46 AM  
**To:** Powers, Christina; Kirrane, Ellen; Luben, Tom  
**Cc:** Lee, Janice; Sams, Reeder  
**Subject:** RE: Revised draft of the June bimonthly materials for iAs

Hi Christy, Ellen, and Tom,

Happy Wednesday (again)!

Thanks for your reviews. I will emphasize that you all LOVED the pictures and that you just couldn't imagine the presentation without them. ☺ But I'm sure they will be cut upon further review.

And Christy, those discussion points in your comments are spot on – make sure they come up during the discussions!

Have a great afternoon!

John

John Cowden, Ph.D.  
Hazardous Pollutant Assessment Group (HPAG)  
National Center for Environmental Assessment (NCEA)  
U.S. Environmental Protection Agency - RTP  
(919) 541-3667

**From:** Powers, Christina  
**Sent:** Wednesday, June 11, 2014 10:53 AM  
**To:** Kirrane, Ellen; Luben, Tom; Cowden, John  
**Cc:** Lee, Janice; Sams, Reeder; Powers, Christina  
**Subject:** RE: Revised draft of the June bimonthly materials for iAs

I agree- great slides!

I have a few relatively minor comments on slides 10, 12, and 13. Most of the comments relate to details that I'm guessing you plan to say already, but wanted to make sure.

As always, let me know if any of the comments are unclear, or if you'd like to discuss.

Thanks!  
Christy

Christy Powers  
Postdoctoral Fellow  
National Center for Environmental Assessment (B 220-I)  
Office of Research and Development  
U.S. Environmental Protection Agency  
Research Triangle Park, NC 27711

Tel: (919) 541-5504

E-mail: [powers.christina@epa.gov](mailto:powers.christina@epa.gov)

Notice (If This Communication Regards a Contract): Nothing in this message shall be construed as a change to the price, schedule, or terms and conditions of the contract. If the receiver does construe it otherwise, please notify me immediately so that proper contract action can be initiated.

**From:** Kirrane, Ellen  
**Sent:** Wednesday, June 11, 2014 9:48 AM  
**To:** Luben, Tom; Cowden, John; Powers, Christina  
**Cc:** Lee, Janice; Sams, Reeder  
**Subject:** RE: Revised draft of the June bimonthly materials for iAs

I agree – very nice slides. Clear and well-organized (and visually appealing!).

**From:** Luben, Tom  
**Sent:** Wednesday, June 11, 2014 9:42 AM  
**To:** Cowden, John; Kirrane, Ellen; Powers, Christina  
**Cc:** Lee, Janice; Sams, Reeder  
**Subject:** RE: Revised draft of the June bimonthly materials for iAs

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The only other change was on slide 8. I changed the text in one of the sub-bullets from "selecting studies" to "characterizing studies". "Selecting studies" made it sound like we were excluding some studies, which we would clearly never do.

Thanks,

Tom

**From:** Cowden, John  
**Sent:** Wednesday, June 11, 2014 9:25 AM  
**To:** Luben, Tom; Kirrane, Ellen; Powers, Christina  
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**Subject:** FW: Revised draft of the June bimonthly materials for iAs

Hi Christy, Ellen, and Tom,

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Let me know if you have any questions. Have a great afternoon!

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National Center for Environmental Assessment (NCEA)  
U.S. Environmental Protection Agency - RTP  
(919) 541-3667

**From:** Cowden, John  
**Sent:** Friday, June 06, 2014 5:00 PM  
**To:** Lee, Janice  
**Cc:** Jones, Samantha; Sams, Reeder  
**Subject:** Revised draft of the June bimonthly materials for iAs

Hey Janice,

Happy Friday! I hope that things are going well for you today.

I made a bunch of changes to the initial draft presentation, mostly because "All text on white background make John a dull boy." Plus, that IRIS painting is terrible. ☺ I cc'd Samantha just so she's aware that we're about done (you know how she is)! ☺ Besides, we will need Reeder's input anyway. A few text changes/formatting refinements and I think we'll be good to go. Oh, and we want to be CRYSTAL CLEAR to Samantha that Catherine/chromium should NOT have to follow this format. I certainly don't want to put more work on her plate. We're just doing what works for us.

I tried to piece together a few key areas for discussion on the science issues. I think Science questions 4 and 5 could be combined together - there are only minor differences between upstream events and concordance, right?

Feel free to revise. Have a great weekend!

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**Bohn, Brent**

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**From:** Powers, Christina  
**Sent:** Wednesday, June 11, 2014 10:53 AM  
**To:** Kirrane, Ellen; Luben, Tom; Cowden, John  
**Cc:** Lee, Janice; Sams, Reeder; Powers, Christina  
**Subject:** RE: Revised draft of the June bimonthly materials for iAs  
**Attachments:** IRIS June Bimonthly Public Meeting\_arsenic - draft - jc edits - 06.06.14\_CP.pptx

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**Cc:** Lee, Janice; Sams, Reeder

**Subject:** RE: Revised draft of the June bimonthly materials for iAs

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(919) 541-3667

**From:** Cowden, John

**Sent:** Friday, June 06, 2014 5:00 PM

**To:** Lee, Janice

**Cc:** Jones, Samantha; Sams, Reeder

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491  
**Bohn, Brent**

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**Bohn, Brent**

493

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**Cc:** Lee, Janice; Sams, Reeder  
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**Attachments:** IRIS June Bimonthly Public Meeting\_arsenic - draft - jc edits - 06 06 14\_tjl.pptx

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**Bohn, Brent**

494

**From:** Cowden, John  
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**To:** Luben, Tom; Kirrane, Ellen; Powers, Christina  
**Cc:** Lee, Janice; Sams, Reeder  
**Subject:** FW: Revised draft of the June bimonthly materials for iAs  
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**Bohn, Brent**

495

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**From:** Powers, Christina  
**Sent:** Tuesday, June 10, 2014 11:35 AM  
**To:** Sams, Reeder  
**Cc:** Powers, Christina  
**Subject:** RE: Public Comments and logistics for Bimonthly on Arsenic

Hi Reeder,

I wanted to check in with you on whether I should initiate any travel paper work to attend the bimonthly, or if you would prefer to wait until after our discussion on Thursday? I anticipate that we'll have a much better idea of who would be most useful to have onsite after Thursday's discussion, but just wanted to make sure I wasn't a source of any lag in planning.

Thanks!  
Christy

-----Original Appointment-----

**From:** Sams, Reeder  
**Sent:** Tuesday, June 10, 2014 11:28 AM  
**To:** Sams, Reeder; Cowden, John; Powers, Christina; Gift, Jeff; Luben, Tom; Lee, Janice; Andrew Rooney; Kirrane, Ellen  
**Subject:** Public Comments and logistics for Bimonthly on Arsenic  
**When:** Thursday, June 12, 2014 3:00 PM-4:00 PM (UTC-05:00) Eastern Time (US & Canada).  
**Where:** RTP-B230-Max20-NCEA/RTP-Bldg-B

To all:

For the arsenic materials we released for the June Bimonthly meeting are due June 11<sup>th</sup> from stakeholders. If you have time to take a cursory look at these tomorrow afternoon or Thursday that would be great but not necessary. We need to meet shortly to agree on who will take the lead for specific comments and prepare for the meeting on June 25<sup>th</sup>-27<sup>th</sup>.

Call in: 1-866-299-3188; conf code:919-541-0661

Best Regards,  
Reeder

**Bohn, Brent**

498

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**From:** Sams, Reeder  
**Sent:** Friday, April 19, 2013 12:45 PM  
**To:** Cowden, John; Lee, Janice  
**Subject:** ADP  
**Attachments:** iAs Assessment Development Plant - draft - 04 19 13 (2).docx  
**Categories:** Record Saved - Private

John and Janice,

Attached is the current draft of the ADP. I have made it through Section 4 and am starting to go through Section 5. In Section 5.5.1.2 it has a note to check with Ryan, does this text need revised? Also, I tried to revise the figure titles in Section 4, but it would not allow me to go to the original file. My plan is to send out hopefully today or before Monday.

Best Regards,  
Reeder

Reeder L. Sams II, Ph.D.  
Deputy Director (Acting)  
Research Triangle Park Division  
National Center for Environmental Assessment  
Office of Research and Development  
U.S. Environmental Protection Agency, B243-01  
RTP, NC 27711

Phone: 919-541-0661  
Fax: 919-541-0245

499  
**Bohn, Brent**

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**From:** Cowden, John  
**Sent:** Thursday, May 16, 2013 2:50 PM  
**To:** Lee, Janice  
**Subject:** ADP draft edits  
**Attachments:** iAs Assessment Development Plant - draft - jc - 05.16.13.docx  
**Categories:** Record Saved - Private

Hey Janice,

Happy Thursday! I hope that things are going well for you today.

Here is the latest version of the ADP with my attempt at revisions. Feel free to make any revisions you want, then send the thing on to Reeder.

Let me know if you have any questions. Have a great afternoon!

John

John Cowden, Ph.D.  
Hazardous Pollutant Assessment Group (HPAG)  
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(919) 541-3667

**Bohn, Brent**

500

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**From:** Lee, Janice  
**Sent:** Tuesday, March 19, 2013 3:10 PM  
**To:** Cowden, John; Sams, Reeder  
**Subject:** ADP with hazard ID edits  
**Attachments:** iAs Problem Formulation Statement - draft - concept model + analysis plan - 03 19 13 \_JL.docx

**Categories:** Record Saved - Private

Wasn't sure how much detail to put in there. And there seems to be a lot of overlap with the conceptual model. Not sure if this is what you want, just let me know.

Janice

**Bohn, Brent**

501

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**From:** Lee, Janice  
**Sent:** Tuesday, February 11, 2014 9:53 AM  
**To:** Cowden, John  
**Subject:** ADP  
**Attachments:** iAs Assessment Development Plan - revised draft - 02 06 14.docx  
**Categories:** Record Saved - Private

Hi John,

Here is the ADP with my revisions.

Let me know what time you're meeting with ICF today. I may be done with the industry meeting early. Guess it depends how much they push back.

Janice

**Bohn, Brent**

502

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**From:** Turley, Audrey <Audrey.Turley@icfi.com>  
**Sent:** Wednesday, May 08, 2013 9:55 AM  
**To:** Lee, Janice; Cowden, John  
**Cc:** Henning, Cara; Eftim, Sorina; Blain, Robyn  
**Subject:** Arsenic - 2 Example Study Quality Entries  
**Attachments:** Study Quality - epiDRAGON\_2 Example Bladder Cancer Entries 050813.pdf

**Categories:** Record Saved - Private

Hi John and Janice,

Here are two examples of study quality entries for studies reporting bladder effects. Hopefully these will be helpful for later!

Kudos to Sorina and Robyn for tackling these yesterday.

Audrey

**AUDREY TURLEY |**  
**ICF INTERNATIONAL |**